REMARKS

According to Applicants' file, Claims 9-13, 20, 37-56, 58-75, 112-116, and 121-129 were under examination in this application at the time of the Office Action (Paper No. 14), dated November 27, 2002. Applicants respectfully request correction of the record (see, Office Action Summary of Paper No. 14).

Amendments

Applicants have amended Claim 9 to make clear that in the claimed process for isolating nucleic acids from a sample, the step of immobilizing nucleic acids on a non-siliceous surface, i.e., step (b), is carried out in the presence of two component compounds:

(i) a compound selected from the group consisting of a salt of a metal and/or ammonium cation with a mineral acid, a salt of a mono or polybasic or polyfunctional organic acid with an alkaline or alkaline-earth metal, a chaotropic agent, and combinations thereof, and

(ii) a hydroxy compound

Thus, step (b) of the isolation process of Claim 9 employs two component compounds, i.e., (b)(i) and (b)(ii) to reversibly immobilize a nucleic acid to a non-siliceous surface. Support for the process employing both (b)(i) and (b)(ii) component compounds is found in the specification (for (b)(i) component, see, e.g., p. 17, line 1-p. 18, line 5, of the specification; for (b)(ii) component, see, e.g., p. 18, lines 6-13, of the specification; studies employing representative species of both components, see, Examples 1-30, e.g., in Example 1, p. 30, lines 12-17; in Example 2, p. 32, lines 9-16; of the specification). Accordingly, the amendment adds no new matter.

Applicants have also amended a number of claims to adjust syntax or to provide additional context or reference for the particular embodiment specified in those claims with respect to the claim from which of they depend. Thus, these amendments to the claims add no new matter:

Claims 40 and 41 were amended to expressly state that the recited solution(s) is an "elution agent in step (c) of the process" of Claim 9.

Claims 46 and 49 were amended to clearly cover embodiments of the process of Claim 9 wherein aqueous solutions of specified salts are employed in step (b) of the process.

Claims 47 and 48 were amended to specify in a Markush group particularly preferred species of aqueous salt solutions useful in the process according to Claim 46.

Claim 50 was amended to clearly specify preferred species of the classes of aqueous salt solutions useful in the process according to Claim 49.

In addition, Claims 51, 52, and 53 were amended to provide a better syntax and clearly recite a specific preferred embodiment of a process according to Claim 49 or Claim 50.

Claims 54, 55, 58, and 59 were amended to expressly indicate preferred compound(s) that are employed in step (b) of the process recited in independent Claim 9.

Claims 61, 62, and 63 were amended to expressly indicate that the recited concentration ranges are applied to aqueous solutions of the chaotropic agent of Claim 59.

Claim 112 was amended to expressly indicate that the recited preferred materials are employed as the non-siliceous surface in step (b) of Claim 9.

Claims 113-115 were amended to maintain consistent use of terms (i.e., "process") throughout the claims.

Entry of the amendments to the claims is respectfully requested.

Foreign Priority Documents

Applicants acknowledge that the Examiner is aware of Applicants' claim of priority under 35 USC § 119(b) and that they may be required to provide further documentation to perfect their priority claim in the future.

Rejection Under 35 USC § 112, First Paragraph

In the Office Action of November 27, 2002, the Examiner rejected Claims 9-13, 20, 37-56, 58-75, and 112-129 under 35 USC § 112, first paragraph, as not supported by an enabling disclosure. In particular, the Examiner stated:

> "As presently worded, the method of claims 9-13, 20, 37-56, 58-75, and 112-129 encompass reversible immobilization of any and all nucleic acids to any non-siliceous surface. The claimed method also encompasses performing such a feat where there can be virtually any amount, or concentration of one or more compounds selected from the following 'a ***salt*** of a metal and/or ammonium cation with a mineral acid, a ***salt*** of a mono or polybasic or polyfunctional organic acid with an alkaline or alkaline-earth metal, a phenol or polyphenol, [and] a chaotropic agent.' As

> presently worded, the nucleic acid(s) could be in an otherwise pure solution of these 'selected compounds'. ***Given that nucleic acids will undergo denaturation as well as degradation when subjected to acids and bases,*** the ability of one of skill in the art to effect such an immobilization over the full breadth of scope is most doubtful." (Section 5, pp. 2-3, of the Office Action; emphasis added).

For the reasons discussed below, Applicants respectfully traverse the rejection.

Applicants first note that the above quote from the Office Action appears to indicate that the Examiner is concerned that the claims specify an incubation of nucleic acid in an acid or base: ***they do not.*** Persons skilled in this art understand nucleic acid chemistry and the ability of certain compounds to denature or, of relevance here to the Examiner's comments, ***degrade*** a nucleic acid, e.g., a strong base, such as sodium hydroxide, can degrade RNA into nucleotides. No essential step of Applicants' claimed process for isolating a nucleic acid calls for combining or incubating a nucleic acid with a destructive acid or base. Applicants believe the source of misunderstanding is the recitation of particular ***components of salts*** that are specified in the specification and claims. For example, as noted in the specification:

> "Suitable ***salts*** for the immobilization of nucleic acids on membranes and other surfaces and/or for the lysis of nucleic samples are ***salts of*** metal cations, such as alkaline or alkaline earth metals, with mineral acids; especially alkaline or alkaline-earth halides and/or sulfates or phosphates, including the halides of sodium, lithium or potassium or magnesium sulfate, which are most preferable. Other metal cations, e.g., Mn, Cu, Cs or Al, or the ammonium cation can be used, ***preferably as salts of mineral acids***.
>
> "Furthermore to carry out the process according to the invention, ***salts*** having one or more basic functions or even polyfunctional organic acids ***with*** alkaline or alkaline-earth metals are suitable. These especially include sodium, potassium or magnesium salts with organic dicarboxylic acids, such as e.g., oxalic acid, malonic or succinic acids, or with hydroxy and/or polyhydroxycarboxylic acids, such as, e.g., with citric acids, preferably." (p. 17, lines1-11, of the specification; emphasis added).
>
> "***The salt solutions used in the processes according to the invention for lysis, binding, washing and/or for elution are preferably buffered.*** All suitable buffer systems can be considered as buffered substances, such as, e.g., carboxylic acid

> buffers, especially citrate buffers, acetate buffers, succinate buffers, malonate buffers as well as glycine buffers, morpholino-propane-sulfone-acids (MOPS) or Tris (hydroxymethyl) ammonium . . . (p. 17, line 30-p. 18, line 3, of the specification; emphasis added).

The above excerpts from the specification make it clear to persons skilled in this art that salts, not free acids or bases, are employed in the invention. Persons skilled in this art would fully understand that "salt" may be described as a salt of a cationic species ***with*** an acid species (see above, e.g., first paragraph of excerpt from p. 17, lines 1-11, of the specification) or, alternatively, of an acid species ***with*** a cation species (see above, e.g., second paragraph of excerpt from p. 17, lines 11, of the specification). A variety of examples in the specification make it clear that the claimed isolation process may employ salts having a particular or preferred cationic component and an acid component for use in the step of reversibly immobilizing nucleic acids on a non-siliceous surface, such as:

> sodium acetate and lithium chloride in Example 2 (p. 32, line 11, of the specification);
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> magnesium sulfate and sodium citrate in Example 10 (p. 44, line 5, of the specification);
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> sodium citrate binding in Example 17 (p. 49, line 13, of the specification);
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> sodium chloride, potassium chloride, or magnesium sulfate with and without ethanol in Example 18 (p. 50, line 10, and Table 11 on pp. 50-51, of the specification);
>
> sodium citrate or sodium oxalate binding buffers in Example 19 (p. 51, line 8, and Table 12 on p. 52, of the specification) and Example 20 (Table 13, of the specification);
>
> sodium citrate, sodium acetate, potassium acetate, ammnonium acetate, malonate, or succinate binding buffers in Example 20 (Table 13 on pp. 53-54 of the specification).

Accordingly, persons skilled in this art who read Applicants' specification would fully understand that the claimed nucleic acid isolation process comprises the use of ***salts***, which are made of certain preferred component metal or other (e.g., ammonium) cations with certain preferred component acids and, further, that the specification and claimed processes would not

and do not comprise the use of compounds that are known in nucleic acid chemistry to degrade or otherwise irreparably damage a nucleic acid.

On another point, Applicants note that the Examiner mentioned that some compounds may have the potential to ***denature*** a nucleic acid in a sample (see above quote from the rejection in Section 5 of the Office Action). As explained above, Applicants' process does not use compounds that would ***degrade*** a nucleic acid of interest, however, that a compound employed in the claimed method might "***denature***" a nucleic acid is clearly ***not*** of particular concern in the claimed process, as indeed, a number of known chaotropic agents, which may denature (but not degrade) some portion of a nucleic acid, work well in Applicants' claimed process for isolating nucleic acid from a sample (see, e.g., p. 17, lines 22-29; Example 1, p. 30, line 5-p. 31, line 23, of the specification). Thus, use of chaotropic agents are known by persons skilled in this art to be compatible with various solutions of nucleic acids, and such agents clearly do not prevent the reversible binding (i.e., immobilization and elution) to a non-siliceous surface according to Applicants' invention. Accordingly, when employed according to the invention, a chaotropic agent, which may have the potential to promote reversible denaturation of a nucleic acid of interest, is in fact demonstrated to be a useful and desired component of, and not a danger to, Applicants' claimed process of isolating a nucleic acid.

In view of the above comments, Applicants submit that the claims are clearly supported by the specification to the extent required by 35 USC § 112, first paragraph. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejections Under 35 USC § 112, second paragraph, and USC § 101

In the Office Action, the Examiner also rejected Claims 40, 41, 46-54, 58, 62, 63, 113-116, 122, and 123 under 35 USC § 112, second paragraph, and 35 USC § 101. The Examiner mentioned that these claims do not set forth any steps involved in the process and therefore are unclear (under 35 USC § 112, second paragraph) as to what process is intended, and, therefore, do not recited a proper process claim (under 35 USC § 101). Applicants respectfully traverse the rejections for the reasons provided below.

All of the claims rejected by the Examiner directly or indirectly depend from independent Claim 9. Claim 9 clearly recites each step in which various material(s) or compound(s) are employed. Applicants are entitled to one or more additional dependent claims that refer back to

and further modify a prior claim, without repeating the entire prior claim (37 CFR § 1.75; MPEP § 608.01(i), (n)). Hence, a person skilled in this art need only refer to Claim 9 or another claim depending therefrom to determine the appropriate context of the particular feature recited in a subsequent dependent claim. Nevertheless, as noted above, Applicants have amended certain dependent claims in order to provide additional or alternative phrasing that refers to an affirmative step or a compound originating in independent Claim 9 (e.g., expressly referencing step (c) of Claim 9 in Claims 40 and 41 or step (b) of Claim 9 in Claims 46, 49, 54, 55, 58, 59, and 112). Further amendments indicate preferred embodiments for elements of Claim 9 or another claim depending therefrom, or maintain consistent use of terms throughout the claims.

In view of the above comments and the amendments to provide express reference to specific steps or compounds in Claim 9, Applicants respectfully submit that the claims are clear and definite, and properly recite subject matter, i.e., a process, which may be patented under the patent law. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the objections to Claims 40, 41, 46-54, 58, 62, 63, 113-116, 122, and 123 under 35 USC §§ 112, second paragraph, and 101.

Rejections Under 35 USC § 103(a)

In the Office Action, the Examiner rejected Claims 9-13, 20, 37-50, 52, 58, 65, 112, and 125-129 as obvious over U.S. Patent No. 4,798,789 (hereinafter, "Lee"). In particular, the Examiner referred to a description in Lee of a protocol that was followed to isolate poly dT-tailed DNA using an oligo (dA)-cellulose column:

> "The dT-tailed DNA was further purified by absorption and elution from an oligo (dA)-cellulose column as follows: The DNA was dissolved in 1 ml of 10 mM Tris.HCl pH 7.3 buffer containing 1 mM EDTA and 1M NaCl, cooled at 0°C., and applied to an oligo (dA)-cellulose column (0.6 by 2.5 cm) equilibrated with the same buffer at 0°C. The column was washed with the same buffer at 0°C, and ***eluted with water at room temperature.*** The eluted DNA was precipitated with ethanol and dissolved in 10 mM Tris.HCl pH 7.3 with 1 mM EDTA." (col. 14, lines 15-27, of Lee; emphasis added).

The Examiner noted that he considered the aspect of having the immobilized dT-tailed DNA on a column that had been chilled to 0°C prior to the introduction of water at room temperature to

elute the dT-tailed DNA to meet the limitation that elution be performed within the temperature limitation of step (c) of Claim 9. Applicants respectfully traverse the rejection for the reasons provided below.

The above excerpt from Lee describes a standard, direct affinity method for separating a nucleic acid from a mixture. According to Lee, a nucleic acid of interest must be subjected to an *in vitro* covalent modification to add a homopolymeric sequence, i.e., a poly dT-tail of 60-80 deoxythymidine residues (see, col. 13, lines 58-60, of Lee), which specifically binds by complementary base pairing to a homopolymeric (poly dA) sequence of a second, known nucleic acid molecule, i.e., oligo (dA) attached to cellulose particles. In contrast, Applicants' claimed process for isolating a nucleic acid of interest does not employ or rely on a covalent modification to alter the sequence of the nucleic acid and does not depend on the presence of a complementary second nucleic acid that serves as an essential reagent for carrying out the isolation process. In particular, according to Applicants' claimed process, a nucleic acid sample is simply applied to and reversibly immobilized on a non-siliceous surface in the presence of: (i) a particular salt compound, chaotropic agent, or a mixture thereof, and (ii) a hydroxy compound (e.g., an alkanol or a phenol). Thus, unlike the method described in Lee, Applicants' claimed isolation process clearly preserves the original structure and sequence of a nucleic acid of interest and does not employ a second, homopolymeric (poly dA) nucleic acid to achieve immobilization and isolation of the nucleic acid of interest.

Furthermore, nowhere in the description of using an oligo (dA)-cellulose column does Lee teach or suggest reversibly immobilizing a nucleic acid of interest to a non-siliceous surface using two particular component compounds as required in Applicants' Claim 9, i.e.,

> (i) a compound selected from the group consisting of a salt of a metal and/or ammonium cation with a mineral acid, a salt of a mono or polybasic or polyfunctional organic acid with an alkaline or alkaline-earth metal, a chaotropic agent, and combinations thereof, and
>
> (ii) a hydroxy compound.

Lee only describes dissolving dT-tailed DNA in a standard high salt hybridization buffer containing 10 mM Tris/HCl (pH 7.3), 1 mM EDTA, and 1 M NaCl to promote complementary base pairing of the homopolymeric sequences of the dT-tailed DNA and the oligo (dA)-cellulose column (see, col., 14, lines 15-20, in Lee). Applicants submit that it is not possible to discern

how a person of ordinary skill in this art would be able to arrive at Applicants' claimed process from the teaching of Lee, which does not even mention the reagents required for carrying out Applicants' process. Clearly, the process in Lee is distinctly different than Applicants' claimed process.

Finally, with respect to the Examiner's view that the temperature for eluting dT-tailed DNA from the oligo (dA) cellulose in Lee may overlap with that employed in Applicants' claimed process, Applicants respectfully submit that a fair reading of the protocol in Lee (see, above) would indicate to persons of ordinary skill in this art that the elution of dT-tailed DNA that is bound to oligo (dA) cellulose was indeed carried out at room temperature, e.g., around 25°C, at which hydrogen bonding of complementary base paired nucleotides (dA;dT), would be ***more destabilized*** than at a lower temperature, as in Applicants' process. This point is further supported by technical information provided from Amersham Biosciences (Piscataway, NJ) (Exhibit A). The oligo (dA) cellulose product formally available from Amersham Biosciences (Piscatway, NJ) has been superceded by poly(A)-SEPHAROSE 4B. In the section of the technical directions entitled "Elution" (see, bottom of p. 1-top of p. 2 of Exhibit A), the directions state with respect to bound nucleic acids:

> "*Nucleic acids*
> Conditions that destabilize hydrogen bonds, such as formamide, ***increased temperature***, or increased ionic strength" (emphasis added)

Accordingly, Applicants submit that the above comments and Exhibit A show that the description in Lee for preparing and isolating dT-tailed DNA using oligo (dA) cellulose would lead a person of ordinary skill in this art to chemistry and conditions that are distinctly different from those employed in Applicants' claimed process.

In summary, Applicants respectfully submit that the above discussion clearly shows that a person of ordinary skill in this art who reads Lee is directed to employ chemistry and reagents that are completely distinct from those employed in Applicants' claimed method for isolating nucleic acids from a sample. In other words, a person of ordinary skill in the art is not directed toward a procedure even remotely resembling the claimed process by following Lee. Accordingly, Applicants respectfully submit that Lee clearly provides no teaching or suggestion of the claimed process of this invention and, thus, does not provide a *prima facie* case of

obviousness under 35 USC § 103(a). Reconsideration and withdrawal of the rejection are therefore respectfully solicited.

Conclusion

In view of all of the above comments, Exhibit A, and the amendments herein, Applicants respectfully submit that the Claims 9-13, 20, 37-56, 58-75, and 112-129 are in condition for allowance. Accordingly, the Examiner is respectfully requested to enter the amendments, withdraw the rejections, and pass this application to issue.

Respectfully submitted,

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